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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	1372.623.PRCWOUS	5509

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EXAMINER	
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,10 and 12-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,10 and 12-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 6 May 2009 have been entered. Claims 1-2, 4, 7, 10, and 12 - 30 are pending and under examination.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6 May 2009 has been entered.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 2, 4, and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss (U.S. Patent 5,851,832) in view of Sanberg (1997. Soc. Neurosci Abstr 23(1-2):346, abstract 140.9) and Grabowski (1994. Exp Neurol. 127(1):126-136).

This rejection stands for the reasons previously made of record and explained in further detail below. Briefly, Weiss '832 patent teaches methods of treating diseases, including stroke, by administration of the progeny of human neural stem cells. Weiss teaches that 1 – 3 ul of

cells at up 50 x 10^6 cells per ml were administered (see column 62 lines 15 – 40) to rats. This corresponds to up to 150,000 cells per animal. Assuming a weight of about 0.3 kg, this is a dose of 500,000 cells per kg of body weight. Weiss explicitly teaches using burr holes to provide entry to the skull (column 62 lines 30 – 40), which is in point to claim 2. However Weiss does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites", as recited in claims 1 and 17 and does not explicitly teach treatment of humans who have experienced stroke at least 3 hours prior to treatment, as recited in claim 1.

Sanberg teaches that hNT cells, transplanted into the brains of rats who had experienced ischemia-inducing surgery a month earlier, are effective to ameliorate behavioral symptoms of stroke. Sanberg teaches that of the doses tested (5,000 – 40,000 cells administered to adult rats), 40,000 cells was the most effective and 5,000 and 10,000 cells were not effective; 20,000 cells per rat was partly effective. The reference therefore is on point to treating stroke with hNT cells; however Sanberg does not explicitly teach administering the cells to humans and does not teach administration of at least 6 million cells, or a plurality of sites as recited in claims 1 and 17. Further Sanberg does not explicitly teach using a burr to enter the brain as recited in claim 2 and does not teach administration of cells 3 months after the stroke as encompassed by claim 4.

Grabowski et al. teach another model of transplantation in which fetal cortex is grafted into the infarcted cortex of rats that having undergone middle cerebral artery occlusion 5-7 days, 3 weeks, or 8 weeks prior. The reference therefore is on point to treatment of stroke by administration of cells into the brains of affected patients. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. However Grabowski does not explicitly teach waiting at least 3 months as recited in claim 4, and does not teach hNT neuronal cells, does not explicitly teach "a plurality of brain area sites" as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the methods of Weiss, who teaches treatment of stroke by administering neural stem cells and indicates that such treatments will also be effective in humans, by substituting the hNT cells of Sanberg and by waiting at least 5-7 days, as taught by Grabowski. Additionally, it would have been obvious to one of ordinary skill in the art to use at least 6 million cells, given the teachings of both Weiss

and Sandberg. The motivation to do modify the methods of Weiss would be to effectively treat stroke in humans. It would have been reasonable to expect success as well.

Applicant continues to traverse the examiner's determination of obviousness. Specifically, applicant makes the following arguments, each of which will be addressed in turn:

1) One or more elements for a prima facie case of obviousness is missing (remarks filed 6 May 2009, pp. 6 - 13);

2) The cited references teach away from their combination (remarks, pp. 13 - 16); and

3) Given the state of the art, the combination of references would not have yielded predictable results as the rodent model of stroke is not a reasonable model of human stroke.

Applicant's arguments have been fully considered but they are not persuasive. With respect to 1), applicant argues that Weiss fails to teach administration of at least 6 million hNT cells, and that Sanberg and Grabowski fail to cure this deficiency. The examiner concedes that Weiss does not teach administration of this exact number of cells, or of hNT cells. However, Sanberg teaches administration of 20,000 or 40,000 hNT cells to rats was effective in treating stroke. This indicates to one of ordinary skill in the art that hNT cells are effective in treating stroke in rodents, and since Weiss teaches that cells can be used to treat stroke in humans, it would be reasonable to expect success in using the cells from Sanberg in such a method. Furthermore, since a 75 kg person is 250 times the mass of a 0.3 kg rat, one of ordinary skill in the art would reasonably expect that a larger dose should be used. As set forth previously, adjusting the number of cells on the basis of body weight would be reasonable as it is a common practice in the art. Doing so would result in administering more than 6 million cells to a human.

At page 8 of the remarks, applicant argues that 6 million cells is the optimum number of cells to be administered to a human, and that applicant was the first to discover this particular dose. While that may indeed be the case, applicant is not claiming administering exactly 6 million cells. Applicant is claiming a "method comprising delivering at least 6 million viable hNT" cells. As set forth previously, the references taken as a whole point to doses of cells greater than what is claimed. Even assuming, for the sake of argument alone, that the references did not point to exactly the number of cells to be administered, optimizing a dosage is generally not considered to be a patentable treatment (see for example MPEP § 2144.05(II), which states that "[g]enerally, differences in concentration ... will not support the patentability of subject matter encompassed by the prior art"). Given that there is guidance in the art of record on how many

cells should be used to treat stroke in a rat, scaling up that number to treat a stroke in a person would have been obvious to one of ordinary skill in the art.

Applicant also argues that Weiss fails to teach waiting at least 3 hours after stroke before administering cells. Grabowski cures this deficiency. Grabowski very clearly teaches that transplanting exogenous tissue is more effective at longer time intervals. The reference teaches that grafting fetal cortex into the infarcted cortex of rats that having undergone middle cerebral artery is most effective at longer delays, and presents examples of treatment at 5-7 days, 3 weeks, and 8 weeks. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. Therefore this reference guides one of ordinary skill in the art to select a time that is more than three hours after stroke, when administering foreign tissue for treatment of said stroke.

Applicant also argues that none of the cited references teaches administering hNT cells to a plurality of brain sites. While the examiner had conceded such, choosing more than one brain site (that is, a plurality of sites) would have been obvious to one of ordinary skill in the art. Given that strokes were known to induce damage on large brain regions, especially when the stroke is the result of an artery occlusion such as in the prior art references cited, administering to more than one site would have been the result of common sense, not an inventive leap beyond the grasp of an artisan of ordinary skill.

With respect to 2), the examiner can find no specific teaching away from the efficacy of hNT cells in the references cited. In fact, quite to the contrary, Sanberg explicitly teaches that they are effective in treating stroke. Why would one of ordinary skill in the art think this was somehow an inducement not to treat humans? There is no suggestion that the treatment will only be effective in small rodents, and there is no teaching away from modifying Sanberg's method by treating humans rather than rodents. While Weiss teaches that cell lines in general are less than optimal, the express teachings of Sanberg clearly outweigh the general comments of Weiss.

With respect to 3), applicant again argues that the state of the art was such that one of skill in the art could not have reasonably predicted that effective treatments for stroke in rodents would also be effective in humans, as claimed. The examiner believes that this point has been fully developed on the record. Statements that rodent models of stroke were not representative of human stroke fly in the face of common sense, and are contradicted by one of the applicant's

(Sanberg) own publications. For example Borlongan et al. 1998 (NeuroReport 9:2837-2842, cited as reference 25 on the IDS filed 15 November 2002) refers to middle cerebral artery occlusion as a "rodent model of stroke" and notes that it “induces transient, focal cerebral ischemia... and is accompanied by prolonged deficits in learning and memory as well as motor behavior" (p. 2837, second paragraph). Additionally Borlongan et al. 1998 (Experimental Neurology 149:31-320) also refers to rodent middle cerebral artery occlusion as a rodent model of stroke and discusses the similarities between deficits in rodents and humans (p. 3111 first column). Thus applicant's argument that the middle cerebral artery occlusion experiments in rodents have no predictive value and are generally recognized by the art to be of no value appear to be in conflict with Dr. Sanberg's publications. Furthermore, in the reference by Savitz (submitted on the IDS filed 6 May 2009), a brief scan of the cited literature reveals several titles indicating that the art recognized that rodent artery occlusion was a reasonable model of stroke (see titles of citations no. 2, 9, and 21 on p. 413 for example, each of which was published prior to the filing date of the present application). Taken as a whole, an artisan of ordinary skill would have had a reasonable expectation of success in treating humans as claimed rather than rodents as explicitly taught by Sanberg 1997). Although applicant has been able to point to a few references pointing out that rodent models of stroke are not ideal, they were nonetheles the art-accepted model at the time the invention was made. So upon reading the reference by Sanberg 1997, one of ordinary skill in the art would have found it obvious to perform the same method (administration of hNT cells) in humans with a stroke.

For at least the reasons above, the rejection is maintained.

4. Claims 7, 10, 12 – 17, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sanberg (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of Weiss (U.S. Patent 5,851,832) and Uchida (1995. Exp. Neurol 132:194-208).

This rejection stands for the reasons above and those previously made of record. Applicant did not traverse the examiner’s determination that the reference by Uchida renders obvious the limitations drawn to sterility, recited in these claims. Rather applicant argues that the reasons why these claims are non-obvious over the cited art are the same reasons the other claims are non-obvious over the cited art, namely that the art does not lead one of ordinary skill to the number of cells to be administered and does not provide a reasonable expectation of

success. For the reasons set forth in the previous rejection, these arguments are not persuasive.

Applicant also points to a single sentence by Uchida (remarks, middle of p. 22, in bold) suggesting there might be an alternative explanation for the observed movement of cells. However, Uchida discounts this possibility and notes that "care was taken to minimize the possibility of disrupting brain structures" and states that migration of implanted cells is the best explanation for the observed phenomenon (cells seen distant from site of injection).

New Rejections

Claim Rejections - 35 USC § 103

5. Claims 20 - 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dinsmore (U.S. Patent 6,140,116, issued 31 October 2000, filed 7 November 1995) in view of Grabowski (1994. Exp Neurol. 127(1):126-136, of record).

Dinsmore teaches treating stroke in humans by administering fetal pig neurons. See for example abstract, which indicates that stroke should be treated, as well as column 2 lines 40 - 51. The procedures to isolate fetal neurons are detailed throughout the patent. At column 6 lines 14 - 28, Dinsmore teaches that human diseases are to be treated by administering these cells, and that stroke in particular is to be treated, At column 11 lines 40 - 57, Dinsmore teaches that the cells to be transplanted should be neurons, and teaches one of ordinary skill in the art how to select neural cells based on their morphology. Dinsmore teaches one of ordinary skill in the art that 12-20 million cells should be administered to a human subject, including those suffering from neurodegeneration due to stroke. See column 19 lines 2 - 22 and column 19 line 60 - column 20 line 12. Thus Dinsmore teaches every element of claim 20, with the sole exception of the time between the occurrence of stroke and the onset of treatment. Claim 20 requires at least 3 hour delay, which is not explicitly taught by Dinsmore.

However, Grabowski et al. teach another model of transplantation in which fetal cortex is grafted into the infarcted cortex of rats that having undergone middle cerebral artery occlusion 5-7 days, 3 weeks, or 8 weeks prior. The reference therefore is on point to treatment of stroke by administration of cells into the brains of affected patients. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. Note that Grabowski indicates that grafting tissue into patients suffering from stroke was known to

"improve acquisition of spatial alternation behavior in rats" (p. 135 final sentence), which is on point to treating patients with decreases in cognitive function, since this task requires cognitive function. However Grabowski does not explicitly teach administration to humans suffering from stroke, as required by claim 20.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Dinsmore, who specifically teaches treating human patients suffering from stroke by administering at least 12 million fetal pig neurons, by choosing the time delay between stroke and grafting taught by Grabowski, thereby arriving at the invention of claim 20. Choosing this particular delay would not be the result of a patentable contribution meriting a right to exclude others from practicing the claimed invention, but would have been the result of ordinary optimization. The examiner acknowledges that neither reference explicitly teaches that morbidity is reduced for at least a year, as recited in claim 20. However, this is not an active method step that is required by the claim, but rather is a statement of the duration of the beneficial effect. Since the starting materials, patient population, and steps of claim 20 are all rendered obvious by Dinsmore in view of Grabowski, this outcome is provided for.

Claim 21 is included in this rejection as Dinsmore teaches implanting 12-20 million cells, which is "at least six million" cells. Claims 22 - 23 are included as Dinsmore also teaches that bilateral brain degeneration, including such degeneration caused by stroke, can be treated (see column 19 lines 2 - 22 and column 19 line 60 - column 20 line 12). Claim 24 is included in this rejection as Dinsmore teaches that sterotactic injection should be used to administer the cells (column 19 lines 4 - 7). Claim 25 is included in this rejection as it recites an effect or outcome that will occur following the administration of the cells. Claims 26 - 27 are included in this rejection since Dinsmore teaches that transplanting the porcine neural cells (including fetal cells) of the invention replaces lost neurons and "results in reconstitution of damaged neural circuits" (column 20 last paragraph and column 2 lines 41 - 51), and also teaches that in specific preferred forms of the invention, the porcine cells should be modified so that they are non-immunogenic as recited in claim 27 (see column 18 final paragraph). Claim 28 is included as the neurons are fetal pig cells. Claim 30 is included in this rejection as well. Even though Grabowski does not explicitly teach waiting three months between the time of stroke and treatment, the reference teaches that delaying transplantation as long as 8 weeks (two months) is still effective, therefore waiting three months rather than two months would still be obvious, given the explicit teachings of Grabowski.

6. Claims 20 - 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dinsmore in view of Grabowski as applied to claims 20 - 28 above, and further in view of Larazov-Spiegler 1996 (FASEB J. 10:1296-1302).

The reasons why claims 20 - 28 are obvious over Dinsmore in view of Grabowski are set forth above. However neither reference explicitly teaches coadministering macrophages that have been activated by exposure to peripheral nerve cells as recited in claim 29.

Larazov-Spiegler teaches that administering macrophages that have been exposed to a peripheral nerve, in particular sciatic nerve segments, is therapeutic for damaged CNS neurons. See for example abstract, as well as paragraph spanning pp. 1297 - 1298. This is on point to claim 29. However Larazov-Spiegler does not teach treating stroke in humans, as required by independent claim 20.

It would have been obvious to one of ordinary skill in the art to modify the methods rendered obvious by Dinsmore in view of Graboswki to include administration of macrophages activated by peripheral nerves, as taught by Larazov-Spiegler, thereby arriving at the invention of claim 29. Doing so would have been obvious to one of ordinary skill in the art, as each product (the porcine fetal neurons and the activated macrophages) was known to be effective for treating damaged CNS tissue, so coadministering them would have been obvious.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
June 4, 2009